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Pathophysiology of Massive Infantile Spasms: Perspective on the Putative Role of the Brain Adrenal Axis

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Abstract

Massive infantile spasms are an age-specific seizure syndrome of infancy. Uniquely, the spasms respond to hormonal manipulation using adrenocorticotropic hormone (ACTH) or glucocorticoids. A hypothesis explaining the efficacy of hormonal therapy, age-specificity, multiple causative factors, and spontaneous resolution of infantile spasms is presented. Corticotropin-releasing hormone (CRH), an excitant neuropeptide suppressed by ACTH/steroids, is implicated. Evidence for the age-specific convulsant properties of CRH is presented, and a putative scenario in which a stressinduced enhancement of endogenous CRH-mediated seizures is discussed. Clinical testing of the CRH-excess theory and its therapeutic implications are suggested.

Massive infantile spasms (MIS) represent a seizure disorder with unique clinical and electrographic features [1-4]. It is relatively common (1:2,000–4,000 births [5, 6]) and has been known to respond to adrenocorticotropic hormone (ACTH), since 1958 [7]. Long-term intellectual outcome of affected infants, however, remains poor, with 76 to 95% of survivors having moderate to severe mental retardation [1, 3, 6, 8]. Therefore, MIS continues to attract research concerning both pathogenesis and therapy. Several large series [1, 3, 9-11] and recent reviews [6, 8, 12-14] have focused on clinical and electroencephalographic phenomenology of MIS, and on the therapy and outcome aspects of this entity. Here I introduce an age-specific endogenous-convulsant hypothesis for the pathophysiology of MIS. The hypothesis implicates an endogenous neuropeptide, which is known to cause seizures in infant rats, and is suppressed by ACTH and glucocorticoids (GCs). I shall present evidence for this hypothesis, discuss some of its predictions for treatment options, and place it in the context of current therapeutic controversies.

Definition and Description

Infantile spasms were first described by West [15] in 1841. Reports of an infantile myoclonic epilepsy with poor neurodevelopmental outcome appeared in the European literature, under the names West syndrome, Salaam epilepsy, and others. In the 1950s, Gibbs and Gibbs [16] defined hypsarrhythmia as the high-voltage, chaotic electrographic counterpart of MIS. The ictal correlates of the spasms themselves were delineated by Hrachovy and associates [17]. The poor response of infantile spasms to conventional anticonvulsants [1-4] led to the discovery of the efficacy of ACTH in patients with MIS [7], and to the use of this hormone as well as GCs as the major therapeutic agents for this disorder.

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The syndrome of MIS consists of a constellation of myoclonic seizures in an infant, whose EEG pattern is that of hypsarrhythmia or its variants [1-4, 7-11, 14, 17]. The electroencephalographic (EEG) pattern, response to therapy, and poor outcome distinguish MIS from a variety of other myoclonic epilepsies of infancy [1, 18]. Furthermore, MIS is a time-locked entity; it arises in infancy after a delay from the time of insult and, in the majority of cases, disappears spontaneously. Even without treatment, 89% of patients are reported to be spasm free by 5 years of age [19].

Proposed Pathophysiology

MIS develops in infants with a variety of central nervous system (CNS) pathologies [1-4]. Structural anomalies, tuberous sclerosis, and other phakomatoses are commonly associated with MIS. Prenatal as well as peri- and postnatal infections, stroke, trauma, and even chromosomal aberrations have all been implicated as causative factors. This multitude of associated factors has suggested that MIS may be a “final common pathway” or an age-specific yet cause-nonspecific response of the brain [1, 20, 21].

Mechanistic theories for the development of MIS have included autoimmune dysfunction [8], developmental “arrest” [21], and brainstem [8] and unihemispheric dysfunction [22]. Any putative mechanism for MIS must explain, or at least be compatible with, most of the unique features of this seizure disorder. Some of these are: How can a single entity have diverse causes (vide supra)? Why does MIS arise after a period of delay? Why only in infancy? Why does it disappear? Why is MIS associated with profound and lasting cortical dysfunction? Why does it respond to ACTH and GCs?

The efficacy of ACTH and prednisone in elimination of the spasms and normalization of the EEG has been one of the few noncontroversial issues in MIS since the initial report, in 1958, by Sorel and Dusaucy-Bauloye [7]. ACTH and GCs result (in 60–80% of patients) in a complete, sudden, and rapid cessation of overt seizures [1-4, 8, 11], commonly within days [23]. Furthermore, the high-voltage hypsarrhythmic EEG normalizes or is improved. This response to ACTH and steroids is considered an all-or-none phenomenon [2, 4, 8, 10-12],

Several mechanisms may explain the observed efficacy of ACTH and GCs. ACTH and steroids may have intrinsic anticonvulsant properties [24, 25]. Some authors consider ACTH superior to prednisone [23]. The former may act as an anticonvulsant per se [26] or result in higher, more sustained elevation in GC levels [23]. Animal studies regarding the anticonvulsant properties of GCs and ACTH are inconclusive, i.e., both convulsant and seizure-suppressant effects have been reported [24-27]. Few studies have addressed the effects of these compounds in infant animals [26, 28]. Direct effects of GCs on neuronal excitability in the adult have recently been reviewed [25]. GCs may also act indirectly by modulating neurotransmitter or second messenger systems [25]. GCs, acting via specific receptors, modulate the expression of a number of genes in the CNS, and may thus alter neuronal excitability as well [29]. ACTH may accelerate CNS myelination and dendritic formation, and thus may shorten the vulnerable, hyperexcitable epoch of infancy [21].

An alternative explanation of ACTH and GC efficacy in MIS is that both hormones suppress an intrinsic convulsant with inherent neuronal excitation properties. Abundance of this convulsant or its receptors, or receptor sensitivity, are abnormally increased in infants with MIS. The abnormal levels and excitant properties of this hypothetical molecule should be age specific and occur in infancy only. Does a substance fulfilling these requirements exist?

Corticotropin-releasing Hormone and the Brain-Adrenal Axis

Corticotropin-releasing hormone (CRH) is a 41-amino acid neuropeptide isolated originally from the mammalian hypothalamus [30]. In response to a variety of stressful stimuli, the synthesis and secretion of this neuropeptide are increased [31]. CRH acts on the pituitary to promote the release of ACTH, which, in turn, enhances GC synthesis and release from the adrenal. ACTH and GCs act via a negative feedback mechanism to suppress the synthesis and secretion of CRH [31, 32]. This brain-adrenal axis and the negative feedback regulators' effects of ACTH and GCs are shown in Figure 1.

The developmental pattern of CRH gene expression in the rat has recently been elucidated (Fig 2, top panel). CRH synthesis commences during late fetal life, but diminishes significantly perinatally [33, 34]. CRH synthesis remains low during the first postnatal days, then increases to adult levels. The prevalence of CRH receptors (measured by binding studies) in the developing rat brain has a different time course; receptor number is maximal during the first postnatal week [35]. Thus, during the first postnatal week, there is a large number of unoccupied CRH receptors throughout the rodent brain. Maximal receptor concentration is found in laminae III and IV of frontoparietal cortex, cerebellum, and certain brainstem nuclei [36].

Nonendocrine Effects of Corticotropin-releasing Hormone in the Central Nervous System

CRH and its mRNA are distributed in specific CNS regions; outside the hypothalamus, high peptide concentrations are found in the amygdala, inferior olive, and some brainstem nuclei [37, 38]. CRH has excitant properties on a wide variety of neurons in several species [39-44]. In vitro studies of hippocampal slice preparation [39] and in vivo eiectrographic investigations [40-42] amply document that CRH increases neuronal excitability. In adult rats, CRH administered into the cerebral ventricles results in epileptiform discharges in amygdala [41] and hippocampus [42], and 3 to 7 hours later, in overt, “limbic” seizures [41].

We have recently found CRH to be a far more rapid and potent convulsant when administered to infant rats [45, 46]. Seizures occur with a latency of as little as 2 minutes, and with CRH doses as low as 7.5×10^{-12} mol (compared with $1{,}500 \times 10^{-12}$ mol in the adult). The potency of the peptide is inversely related to age, and diminishes rapidly in the “juvenile” versus the “infant” rat [45]. The effects of increased abundance of the endogenous neuropeptide on brain excitability or susceptibility to seizures are not known at the present time.

The CRH-Excess Theory of Massive Infantile Spasms

Various types of injury to the developing brain may be followed by MIS [1, 6, 21]. We suggest that the difference between those injuries that lead to MIS (in symptomatic cases), and those that do not, lies in their effects on CRH gene expression and secretion. Stress has been shown, in laboratory animals, to increase CRH gene expression [47] and secretion [48] and to alter the brain-adrenal axis throughout life [49, 50]. Humans with depression and those with anorexia nervosa have increased CRH levels in the cerebrospinal fluid (CSF), and an abnormal CRH-ACTH-GC axis [51-53].

The presence of individual variability in the response to a variety of stressors is currently being recognized in neonates and infants [54]. The relevance of such variability to short- and long-term health and susceptibility to a number of illnesses is under intense study [54-56]. Abnormally great CRH production, release, or response may thus result from either

abnormal stress in early life, or an aberrant response to common stresses. Hypertrophy, sprouting, and/or hyperfunction of specific CRH-containing neuronal pathways in the brainstem [38] may lead to myoclonic seizures. Such neuronal sprouting response to injury is well established in the hippocampus [57]. A candidate pathway in the case of CRH may be the inferior olivodentatorubral circuit. Injury to afferent (ventral tegmental or dentatoolivary [58]) inpur results, after a delay period, in olivary "hypertrophy" and palatal myoclonus in human adults [59]. The activation of such pathway may require a shorter delay in children [60]. Only some candidate lesions result in hypertrophy and/or myoclonus [58]. CRH is a putative neurotransmitter in the inferior olive in the human and rodent [6l, 62]. CRH inputs to locus ceruleus and is a modulator of rapid eye movement (REM) sleep [63], which is highly abnormal in infants with MIS [8]. Additionally, "overactivated" cortical and limbic CRH-responsive neuronal circuits may underlie the highly abnormal EEG and the global cognitive dysfunction.

Hypothetically, ACTH and GCs could act via suppression of this overabundant or overactive endogenous convulsant, CRH. The developmental decline in the number of CRH receptors, at least in the rodent [35], would predict the eventual resolution of increased CRH-induced neuronal activation. Present information is insufficient to distinguish between two possibilities, i.e., (1) infants with cryptogenic MIS have experienced unusual stresses that lead to sprouting and hyperfunction of CRH-neuronal pathways, and (2) certain traits, genetic or otherwise, of infants with cryptogenic MIS lead to an excessive CRH activation in response to usual, "normal" stresses with subsequent MIS.

Human Evidence for the CRH-Excess Theory of Massive Infantile Spasms

Verification of increased brain levels of CRH in infants with MIS is inherently problematic. Surgical biopsy and autopsy specimens are predominantly from older children with a history of the disorder, at a time when the criteria for MIS are no longer fulfilled [64]. Attempts have been made to measure CSF levels of CRH as well as of ACTH and cortisol, the major human GC. Nalin and colleagues [65] found a reduction in CSF ACTH levels in 15 infants with MIS. We have recently confirmed this finding in 14 patients controlled for age, stress levels, and diurnal hormonal variation [66]. We also demonstrated diminished CSF Cortisol levels in these infants. We found no difference in CSF CRH in infants with MIS when compared with age-matched control subjects. In primates, however, CSF CRH levels do not correlate with those in the hypothalamus [67]. Whether CRH levels in specific brain regions in infants with MIS differ from those of control subjects is unknown.

The complex interactions of CRH, not only with the ACTH-GC axis, but with other neurotransmitters are becoming evident. For example, serotonin (5-HT) plays a major role in myoclonus [68], and chronic administration of ACTH to neonatal rats reduced cortical 5-HT_2 receptor density [69]. Excess 5-HT activity has been proposed as a pathogenetic factor in MIS [69, 70]. CSF studies of neurotransmitter metabolites in CSF of infants with MIS have yielded conflicting results [8, 71-73]. A body of evidence suggests that, in both humans and rodents, 5-HT input from the raphe [74] may regulate the hippocampal input into the negative feedback of the CRH-ACTH-GC axis ([75, 76] and see Fig 1).

Predictions and Perspective for the Therapy of Massive Infantile Spasms

The treatment for patients with MIS remains controversial. Although ACTH and GCs remain the mainstay of pharmacological therapy, they may have little effect on neurological outcome [1-4], Moreover, these hormones have significant, and occasionally fatal, side effects [77]. Other antiepileptic drugs, i.e., nitrazepam [78], valproate [79], and vigabatrin [80], as well as pyridoxine [81] combined with valproate [82], and γ-globulins [83], may have some benefit, especially when used for several months. Few long-term therapy studies

have controlled for rhe natural resolution of MIS [19, 84]. The CRH-excess hypothesis predicts that specific receptor blockers of CRH [85] will arrest MIS. Such agents may prove safer, with fewer side effects than ACTH and GCs [86]. Furthermore, by acting at multiple CNS sites, they may also alter cognitive outcome of affected infants.

Surgical therapy has been found efficacious for a few infants with focal seizures along with MIS, or intractable focal seizures in a child with a remote history of MIS [87, 88]. The causes for MIS range from global CNS dysfunction to highly focal lesions (e.g., stroke [89]). Therapy may address the “symptom,” via the use of anticonvulsants or ACTH/GCs, or, in selected cases, may be successfully directed against the causative or instigating lesion.

In summary, we propose that abnormally increased CRH synthesis and activity, secondary to antecedent injury or stress, results in selective neuronal hyperexcitability during a period with high CRH-receptor abundance. “Hypertrophic” CRH-responsive brainstem circuits could explain the spasms per se. Other CRH-responsive elements may also be deranged, some permanently (via GC receptor alteration?), others transiently (REM sleep). ACTH and GCs suppress CRH synthesis when given to infants with MIS, eliminating spasms, normalizing cortical EEG, but not reversing permanent neuronal alterations.

This hypothesis explains the multitude of MIS causes, and the therapeutic efficacy of ACTH/GC and of strategies for elimination of focal lesions. The hypothesis predicts that compounds blocking CRH receptors, such as α-helical (9-4l)-CRH, may be useful for the therapy of MIS. Finally, though sketchily documented at present, the proposed mechanism provides a testable working hypothesis for MIS, promoting further studies of this unique infantile seizure disorder.

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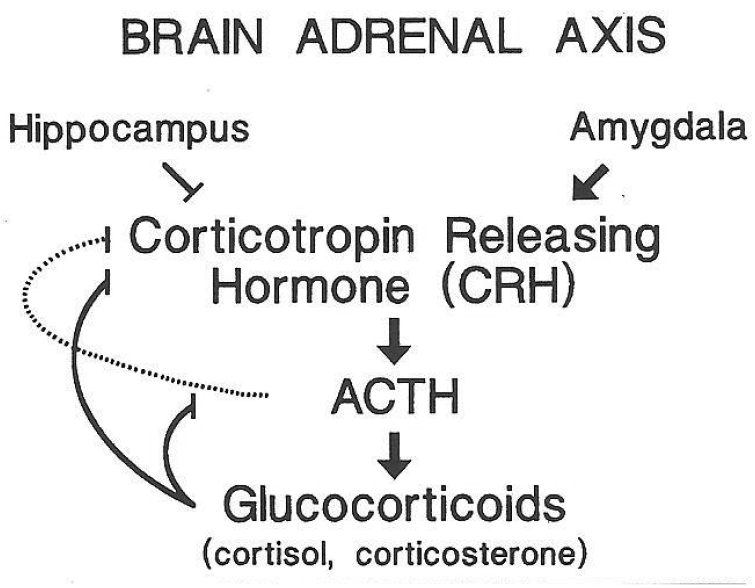

Fig 1.
Schematic of the interactions among the components of the corticotropin-releasing hormone-adrenocorticotropic hormone-glucocorticoid loop. Arrows denote increased synthesis and secretion. Blunt-ended lines denote a suppression of synthesis, release, or both. Broken line implies a putative effect.

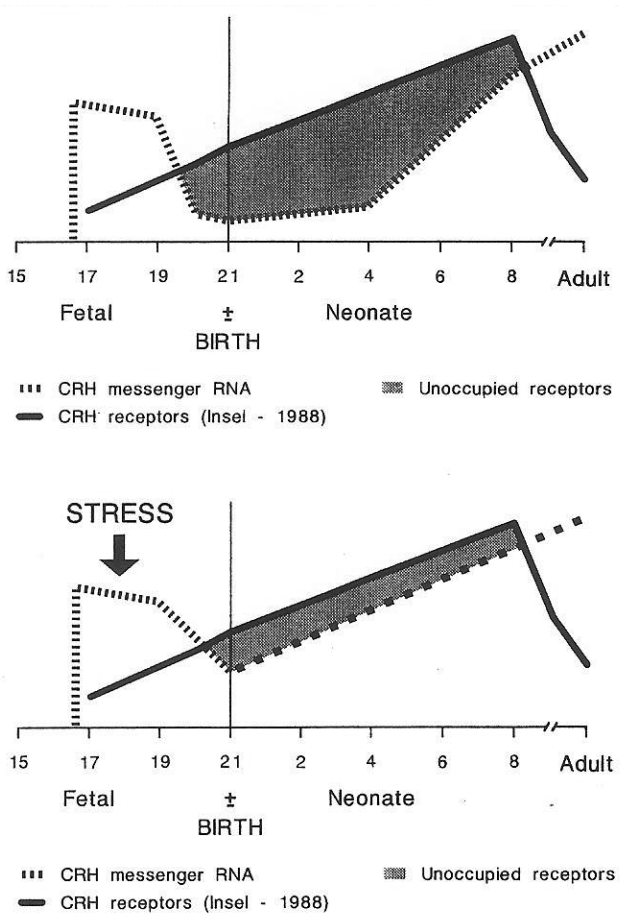

Fig 2.

Graphic illustration of the ontogeny of corticotropin-releasing hormone mRNA (CRH-mRNA) in the hypothalamic paraventricular nucleus in the rat (from {34}). Superimposed is a quantitative analysis of the ontogeny of CRH receptors in rat brain (from {35}, with permission). The top panel demonstrates the observed data. The bottom panel shows the hypothetical effect of stress during late gestation on CRH-mRNA. Birth occurs on the 21st day of gestation. Shaded area = unoccupied CRH receptors.